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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1653	4

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/518,297	Applicant(s) LIM ET AL.	
	Examin r Chih-Min Kam	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nce address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2001* .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 21-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 21-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4, 9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-19 and 21-30 in Paper No. 9 is acknowledged. Non-elected claims 20 and 31-33 have been cancelled.

Informalities

The disclosure is objected to because of the following informalities:

1. The pBK2MC5 construct (SEQ ID NO:44) has the same nucleotide sequence as pBK2MC12 (SEQ ID NO:45) in Sequence Listing Table at page 68 and Sequence Listing. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-19 and 21-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a molecular switch comprising a first nucleic acid construct containing a DNA response element for certain transcriptional regulatory protein operably linked to a first promoter, a compound binding sequence in the vicinity of the DNA response element, a transgene under the control of the first promoter and a DNA binding compound of 21x and GL046732, a cell comprising the molecular switch, and a method of producing a cell having the molecular switch, does not reasonably provide enablement for a molecular switch comprising a first nucleic acid construct containing a DNA response element for any transcriptional regulatory protein operably linked to a first promoter, a compound

binding sequence in the vicinity of the DNA response element, a transgene under the control of the first promoter and any DNA binding compound, a cell comprising the molecular switch, and a method of producing a cell having the molecular switch. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-19 and 21-30 encompass a molecular switch comprising a first nucleic acid construct containing a DNA response element for a transcriptional regulatory protein operably linked to a first promoter, a compound binding sequence in the vicinity of the DNA response element, a transgene under the control of the first promoter and a DNA binding compound (claims 1-15, 21, 23, 25, 27 and 29), a cell comprising the molecular switch (claims 16, 17, 22, 24, 26, 28 and 30) and a method of producing a cell having the molecular switch (claims 18 and 19). The specification, however, only discloses cursory conclusions (page 6, line 27-page 7, line 19), which state that a molecular switch employs a natural, engineered or synthetic DNA binding transcriptional regulatory protein and a compound that interacts with DNA in the vicinity of the transcriptional regulatory protein binding site (or DNA response element), and the binding of the compound to DNA affects the binding of the transcriptional regulatory protein to its DNA response element, thereby modifying the expression of a gene operably linked to the DNA response element, a method of producing cells comprising the molecular switch for modulating gene expression, and cells produced by the method. There are no indicia that the present application enables the full scope in view of a molecular switch, a method of producing cells comprising the molecular switch for modulating gene expression, and cells produced by the method discussed in the stated rejection. The present application provides no indicia and no

teaching/guidance as to how these problems are resolved. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the scope of the claims, the amount of direction or guidance presented and the amount of experimentation necessary as discussed below.

(1). The scope of the claims

Claims 1-19 and 21-30 encompass a molecular switch comprising a first nucleic acid construct containing a DNA response element for a transcriptional regulatory protein operably linked to a first promoter, a compound binding sequence in the vicinity of the DNA response element, a transgene under the control of the first promoter and a DNA binding compound, a cell comprising the molecular switch and a method of producing a cell having the molecular switch. However, the specification only shows a molecular switch employs a DNA binding transcriptional regulatory protein such as UL9-VP16 specific chimeric activator, UL9-KRAB specific chimeric repressor, UL9-NFκBp65, NF-κB and LacR, and a compound such as 21x (dimer of netropsin, pyrrole-containing polyamide) or GL046732 (containing two linked netrospin moiety) that interacts with DNA in the vicinity of the transcriptional regulatory protein binding site, and the binding of the compound to DNA affects the binding of the transcriptional regulatory protein to its DNA response element, thereby modifying the expression of a gene operably linked to the DNA response element, a method of producing cells comprising the molecular switch for modulating gene expression, and cells produced by the method.

(2). The amount of direction or guidance presented and the quantity of experimentation necessary.

The specification indicates the present invention is directed to a molecular switch utilizing a transcriptional regulatory protein and exogenously supplied compound which targets nucleic acid such as the compound binding site in the vicinity of the DNA binding site for a transcriptional regulatory protein in a nucleic acid construct, the binding of the transcriptional regulatory protein may be controlled by the exogenously DNA binding compound (page 16, lines 8-10, lines 17-20). The specification also indicates that the choice of DNA binding domain in a given transcriptional regulatory protein will determine the DNA response element, different DNA response elements can be utilized together with a corresponding DNA binding transcriptional regulatory protein, activator and repressor protein domains may be incorporated into an engineered transcriptional regulatory protein and several examples are given (page 21, line 16- page 24, line 11), and that the preferred compounds include dimers or multimers of some known DNA-binding compounds, peptide nucleic acids, polyamides, and various triplex forming DNA-binding compounds (page 30, lines 13-16). However, the specification does not show the sequence binding preferences for most of these compounds and the binding activities of these compounds toward a specific DNA sequence, in fact, it states that the sequence binding preferences for most known DNA binding molecules have not, to date, been identified (page 30, lines 7-8). The specification does not demonstrate the DNA binding site for compounds such as PNA or other polyamide besides netrospin derivatives, nor indicates such compounds would bind to a compound binding site in the vicinity of the DNA binding site for an identified transcriptional regulatory protein in a nucleic acid construct and affect the binding of the transcriptional regulatory protein to DNA response element that regulates the gene expression. Therefore, it is necessary to have more guidance regarding the identities of the compounds and

trancriptional regulatory proteins, the DNA binding sequence for the compound, the binding abilities of these compounds toward specific sequences, and the DNA binding sites of the trancriptional regulatory proteins in the nucleic acid construct, and to carry out further experimentation to assess the effect of the compounds on the binding of trancriptional regulatory proteins to DNA binding sites in the nucleic acid construct that regulates the gene expression in the molecular switch.

Since it is not routine in the art to engage in *de novo* experimentation where the expectation of success is unpredictable, the skilled artisan would require additional guidance in order to make and use such compounds in a manner reasonably commensurate with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue because the amount of guidance is minimal regarding the identity of molecules and their DNA binding sequences (see above) which leads to the requirement of further experimentation to identify the DNA binding sequences for the compounds and the transcriptional regulatory protein in the nucleic acid construct and to assess the effect of these compounds on the binding of the transcriptional regulatory protein to DNA binding sites in the nucleic acid construct.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-19 and 21-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-19 and 21-30 are indefinite because of the use of the terms "in the vicinity of said DNA response element" and "a DNA binding compound". The terms "in the vicinity of said DNA response element" and "a DNA binding compound" render the claim indefinite; it is unclear what compound is as to a DNA binding compound, and where a compound binding site is located as to the DNA response element, e.g., is the compound binding site adjacent to the DNA response element, or is it a certain number of nucleotides away from the DNA response element,or the two sites are the same? Claims 2-10, 12-17, 19 and 21-30 are included in the rejection because they are dependent on rejected claims and do not correct the deficiency of the claim from which they depend.

4. Claims 1-17 and 21-30 are indefinite because the claim recites the first nucleic acid construct contains (i) a DNA response element, (ii) a compound binding site, (iii) a transgene and (iv) a DNA binding compound, in which the location of the DNA binding compound is not indicated. It is not clear how a DNA binding compound can be part of a nucelic acid construct.

5. Claim 10 is indefinite because of the use of the term "adeno-associated virus vector". The term "adeno-associated virus vector" renders the claim indefinite, it is not clear which vector is as to adeno-associated virus vector.

6. Claim 23 recites the limitation "said regulatory domain" in line 1 and "an activator domain" in line 2. There is insufficient antecedent basis for this limitation in the claim.

7. Claims 14, 29 and 30 are indefinite because of the use of the term "from about.... to...". The term "from about.... to..." renders the claim indefinite, it is not clear how many nucleotides are included in the compound-binding sequence. Use of the term "from....to.." or "about.....to...." is suggested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 3, 5 and 16-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Voet *et al.* (Biochemistry pages 854-856 and 868 (1990)).

Voet *et al.* teach *lac* repressor protein can act as a molecular switch because it specifically binds to the O gene (the operator) to physically block the transcription of mRNA and the protein synthesis of *lac* operon proteins (pages 854-855 and 868, Figures 29-3 and 29-5), wherein the repressor is not only as a transcriptional regulatory protein but also as a DNA binding compound, and DNA response element for the transcriptional regulatory protein is the same as the compound binding site, which meets the criteria of claims 1, 3, 5 and 16-18.

9. Claims 1, 3, 5 and 16-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Gottesfeld *et al.* (Nature 387, 202-205 (1997)).

Gottesfeld *et al.* teach a pyrrole-imidazole polyamide which is cell permeable and binds to a specific region of the transcription factor TFIIIA binding site interferes with the binding of TFIIIA to 5S RNA gene, and it inhibits the RNA polymerase III transcription of a 5S RNA gene

in Xenopus kidney cells (pages 203-205, Figures 1-4), which meets the criteria of claims 1, 3, 5 and 16-18.

10. Claims 1-5, 8 and 16-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Evans *et al.* (U. S. Patent 5,071,773).

Evans *et al.* teach a "cis-trans" bioassay system for testing receptor functionality utilizing two plasmids: an expression plasmid and a reporter plasmid, the expression plasmid is capable of expressing a receptor DNA or a mutant in a receptor-negative host cell and the reporter plasmid contains an operative hormone responsive promoter/enhancer element functionally linked to an reporter gene. The expression plasmid and the reporter plasmid are cotransfected into receptor-negative cells, and the transcription of a reporter gene is activated by hormone complexed with the receptor in the cell (columns 11, 12; column 17, line 36-column 22, line 6), wherein the hormone-receptor complex binds to the DNA response element and acts not only as a transcriptional regulatory protein but also as a DNA binding compound, and DNA response element for the transcriptional regulatory protein is the same as the compound binding site, which meets the criteria of claims 1-5, 8 and 16-17.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 1, 3, 5 and 16-18 are rejected under 35 U.S.C. 102(a) as being anticipated by Dickinson *et al.* (Proc. Natl. Acad. Sci. USA 95, 12890-12895 (1998)).

Dickinson *et al.* teach two pyrrole-imidazole polyamides bind to DNA sequences adjacent to the binding sites for the transcription factors, Ets-1, lymphoid-enhanced binding factor 1 (LEF-1) and TATA-box binding protein (TBP) in the HIV enhancer and promoter. These polyamides specifically inhibit DNA-binding of each transcription factor and inhibit the HIV type 1 transcription *in vitro* (pages 12891-12892, Figures 1-2), when used in combination the polyamides also inhibit virus replication in isolated human peripheral blood lymphocytes (pages 12893-12894, Figures 3-5), which meets the criteria of claims 1, 3, 5 and 16-18.

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D.
Patent Examiner

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October 6, 2001

Christopher S. F. Low
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